Cardiomyopathy

THE HEART IN ANDERSON-FABRY DISEASE AND OTHER LYSOSOMAL STORAGE DISORDERS

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Lysosomal storage disorders (LSD) comprise a group of more than 40 diseases caused by a deficiency of lysosomal enzymes, membrane transporters or other proteins involved in lysosomal biology. The predominant inheritance pattern is autosomal recessive except for Anderson-Fabry disease, glycogen storage disease (GSD) type IIb (Danon disease) and mucopolysaccharidosis (MPS) type II (Hunter disease). While the metabolic defects affect all cells, clinical organ involvement usually occurs only in the presence of substrate excess or metabolic pathway activation. Cardiac disease is particularly important in lysosomal glycogen storage diseases (Pompe and Danon disease), mucopolysaccharidoses and in glycosphingolipidoses (Anderson-Fabry disease). Various disease manifestations may be observed including hypertrophic and dilated cardiomyopathy, coronary artery disease and valvular disease (table 1).

ANDERSON-FABRY DISEASE

Anderson-Fabry disease (AFD, synonyms Fabry disease, α-galactosidase A deficiency, angiokeratoma corporis diffusum) is an X-linked LSD caused by mutations in the gene encoding the lysosomal enzyme α-galactosidase A. The resultant deficiency in α-galactosidase A activity leads to intra-lysosomal accumulation of neutral glycosphingolipids, mainly globotriaosylceramide (Gb_3), in various organ systems. The disease is characterised by progressive clinical manifestations and premature death from renal failure, stroke and cardiac disease.[1]

Epidemiology
The incidence of AFD has been estimated at 1 in 40 000 to 1 in 117 000 live births for males.[1] Recently, studies in high risk patient cohorts suggest that it is much more common. The reported prevalence of AFD in patients with end-stage renal disease on haemodialysis ranges between 0.2–1.2%; in patients with cryptogenic stroke the prevalence may be as high as 4.9% in men and 2.8% in women. The prevalence of AFD in patients with heart disease varies depending on the population studied. In a survey of male patients with unexplained left ventricular hypertrophy (LVH) attending an echocardiography clinic, 3% had biochemical evidence for AFD[2]; in a second analysis of male patients attending a specialist hypertrophic cardiomyopathy clinic, 4% had diagnostic plasma levels of α-galactosidase A.[3] Even higher prevalence figures rates have been reported in studies using endomyocardial biopsy as a screening tool.[4]

Molecular genetics
The α-galactosidase A gene consists of seven exons located on the long arm of the X chromosome (Xq22.1) that encode a 101 kD homodimeric glycoprotein. Over 250 mutations have been described in all seven exons, the majority of which are missense point mutations. Individual mutations are often limited to one or few families (''private mutations'').[5] Reduced enzyme activity occurs by several mechanisms including abnormal or unstable protein folding, perturbation to active binding sites and defective enzyme tracking to the lysosome.[1]

Clinical presentation
The most common clinical features in classical AFD are summarised in table 2. Although many symptoms occur in childhood, correct diagnosis is delayed by as much as 14 years in males and 16 years in females.[1] In males, symptoms start usually in the first decade of life with acroparesthesiae and pain, febrile crises, hypohidrosis, heat intolerance, gastrointestinal disturbance and the development of cutaneous angiokeratomata. From the second decade onwards patients develop proteinuria and neurological manifestations, including vestibular and hearing disturbance and autonomic dysfunction. Cardiac involvement is present early in life but is not detected clinically until the third or fourth decade (fig 1).[1]

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Table 1 Lysosomal storage disease causing cardiac disease

Disease group and subtypes	General manifestations	Cardiac manifestations
Glycogen storage diseases (lysosomal)		
	Autosomal recessive	Massive LVH and RVH, cardiac failure (only in the infantile form)
	Myopathy, hypotonia, hepatomegaly, macroglossia cardiopulmonary failure,	Short PR, broad QRS; endomyocardial fibrosis
Type IIb (Danon disease, LAMP-2 deficiency)	*X-linked*	Hypertrophic cardiomyopathy, isolated cardiac variants, short PR, progressive conduction system disease
	Myopathy, mental retardation	
Mucopolysaccharidoses		
IH (Hurler)	*Autosomal recessive*	Valvular involvement (thickening, regurgitation, stenosis);
IS (Scheie)	*X-linked – MPS II (Hunter)*	endomyocardial infiltration; interstitial infiltration—fibrosis;
II (Hunter)	Dysmorphic features, organomegaly, decreased	hypertrophy; systolic dysfunction—dilated cardiomyopathy (less
III (Sanfilippo)	joint mobility, bone deformities, loss of motor	frequent); coronary artery infiltration—stenosis; aortic stenosis
IV (Morquio)	skills, mental retardation, corneal clouding,	(abdominal); arterial hypertension
VI (Maroteaux-Lamy)	recurrent otitis or pneumonia, hearing loss	
VII (Sly)		
IX (Natowicz)		
Sphingolipidoses		
Gaucher disease (β-glucocerebrodiase)	*Autosomal recessive*	Pulmonary hypertension, cor pulmonale;
Chronic non-neuronopathic (type I)	Gaucher cells—lipid laden macrophages	pericardial effusion (rare); valvular involvement (rare)
Acute (type II)	Hepatosplenomegaly, anaemia,	
	thrombocytopenia, bone involvement	
Chronic neuronopathic (type III)	Neurodegeneration (neuronopathic forms)	
Niemann Pick disease (acid sphingomyelinase)	*Autosomal recessive*	Endomyocardial fibrosis (very rare)
Type A	Early onset, neurological involvement,	
Type B	hypotonia, psychomotor retardation (type A),	
	hepatosplenomegaly, pancytopenia,	
	pulmonary involvement	
Anderson-Fabry disease (α-galactosidase A)	*X-linked*	Cardiac hypertrophy; short PR, progressive conduction system
	Multiorgan involvement	dysfunction, arrhythmias; valvular involvement; coronary involvement (decreased coronary reserve)

LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy.

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Disease in females

Despite early autopsy reports demonstrating clinically significant disease in female heterozygotes, for a long period of time women were considered only as disease carriers. However, many studies have shown that affected women experience symptoms similar to hemizygous males, albeit in a milder form with a delayed onset and slower progression compared to men; similarly, the frequency of end-stage renal disease is much lower and the median cumulative survival greater (70 years vs 50 years) in women.[1] Disease expression in female patients is attributed to random X chromosome inactivation and the incapacity of cells expressing the wild-type allele to cross-correct the metabolic defect.[5]

Pathogenesis of cardiac disease in AFD

Cross-sectional data in patients of different ages suggest that disease evolution in the heart is characterised initially by myocardial hypertrophy; as the disease progresses interstitial abnormalities and replacement myocardial fibrosis become important. This correlates well with observations of relatively mild diastolic dysfunction in early stages of the disease progressing to systolic and severe diastolic ventricular impairment in advanced disease.[6]

Table 2 Main extracardiac clinical manifestations of Anderson Fabry disease

System	Manifestation
► Dermatological	Angiokeratoma
	Hypohidrosis
	Lymphoedema
	Coarse facial features
► Neurological	Neuropathic pain - acroparesthesiae, painful febrile crises
	Autonomic and small fibre dysfunction
	Transient ischaemic attacks, stroke
	Vertigo, tinnitus, hypoacusis, sudden deafness
► Renal	Albuminuria/proteinuria
	Isosthenuria
	Renal failure
► Gastrointestinal	Diarrhoea
	Early satiety
	Abdominal discomfort
► Pulmonary	Airways obstruction
	Decreased diffusion capacity
► Ophthalmologic	Cornea verticellata
	Tortuous retinal vessels
► Other	Anaemia
	Decreased bone density
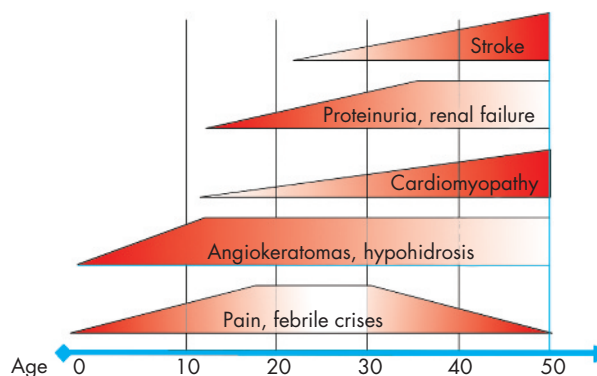
Figure 1 Typical disease course in a classically affected male hemizygote with Anderson-Fabry disease.

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Cardiac disease in AFD is associated with Gb_3 accumulation in all cellular components of the heart, including cardiomyocytes, conduction system cells, valvular fibroblasts, endothelial cells and vascular smooth muscle cells. In women, a mosaic pattern caused by random X chromosome inactivation can be observed.[5] Myocytes are vacuolated and hypertrophied, but unlike familial hypertrophic cardiomyopathy, myofibrillar disarray is not prominent. Lysosomal inclusions are present within myofibrils and vascular structures (figs 2 and 3); fibrosis is evident within the mid-myocardial layers and the posterolateral segments of the left ventricle.[7]

While Gb_3 accumulation is the most prominent feature histologically, it represents only 1–2% of the total cardiac mass.[6] Therefore, it is likely that disease in the heart results from activation of other signalling pathways that lead to hypertrophy, apoptosis, necrosis and fibrosis.

Circumstantial evidence suggests that myocardial ischaemia in the absence of significant disease of epicardial arteries may contribute to disease progression. The underlying mechanisms probably include the increased oxygen demand of the hypertrophied muscle, decreased capillary density and increased diastolic filling pressures; Gb_3 deposition in endothelial and smooth muscular cells of small arterioles and capillaries is another factor.[8]

Specific cardiac abnormalities in AFD
The ''cardiac variant''

A number of reports have suggested that some patients with residual α-galactosidase A activity (approximately 1–5% of normal values) present in middle age with LVH and conduction disease, in the absence of other classical disease manifestations. Some patients with this ''cardiac variant'' had proteinuria, but did not develop end-stage renal disease; they also differed from classical AFD patients in that they did not have glycosphingolipid deposits in vascular endothelium.[2] [3] Contemporary studies suggest that if it exists at all, the cardiac variant of AFD is extremely rare, as rigorous clinical characterisation reveals organ involvement elsewhere. Nevertheless, clinical presentation in patients with residual activity can be dominated by cardiovascular involvement, meaning that AFD should be considered in the differential diagnosis of otherwise unexplained ventricular hypertrophy (table 3).
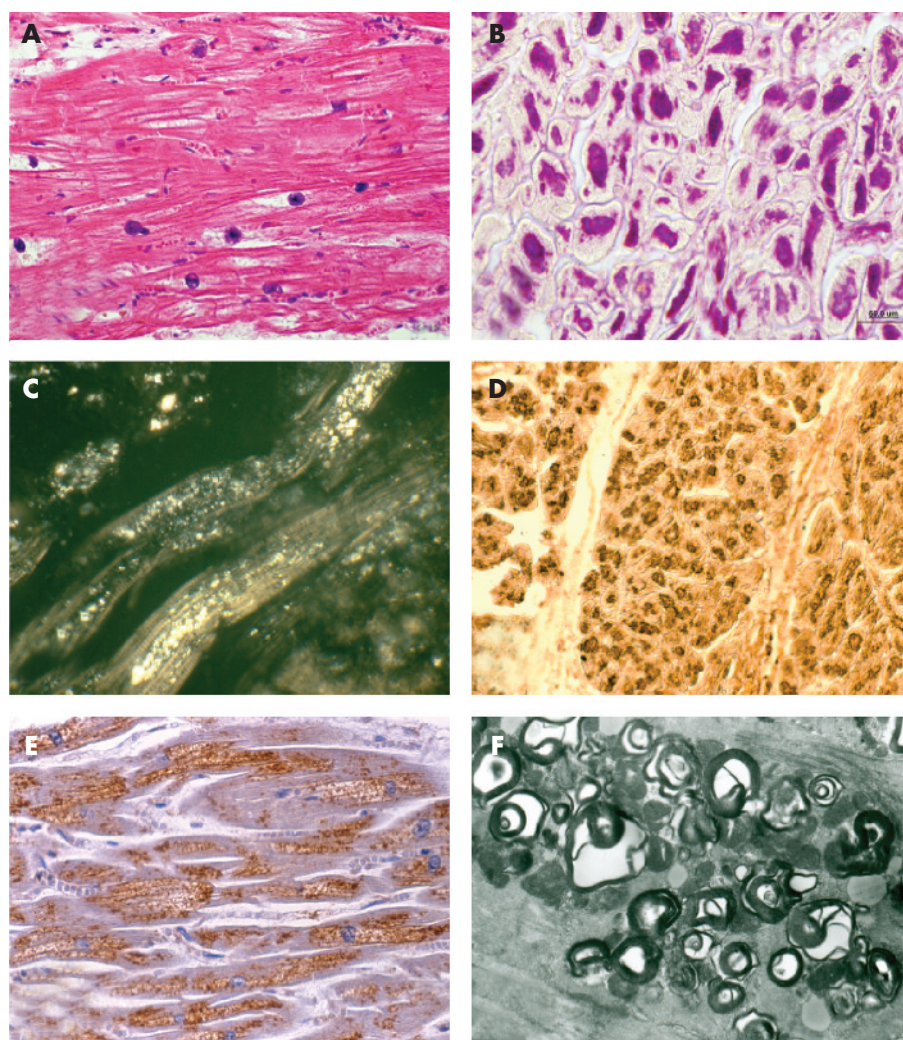

Figure 2 (A) Haematoxylin and eosin staining showing storage (perinuclear vacuoles) and hypertrophy of cardiomyocytes. (B) Glycolipid storage in cardiomyocytes demonstrated by periodic acid-Schiff (PAS) staining of a frozen section. (C) Prominent birefringence of the stored glycolipid liquid crystals. (D) Immunohistochemical staining of the stored glycolipid using antibody against Gb_3Cer. (E) Prominent staining for luminal lysosomal marker cathepsin D in cardiocytes. (F) Electron microscopic ultrastructure of lysosomal glycolipid deposits in a cardiomyocyte. Images courtesy of Milan Elleder, Charles University, Prague, Czech Republic.
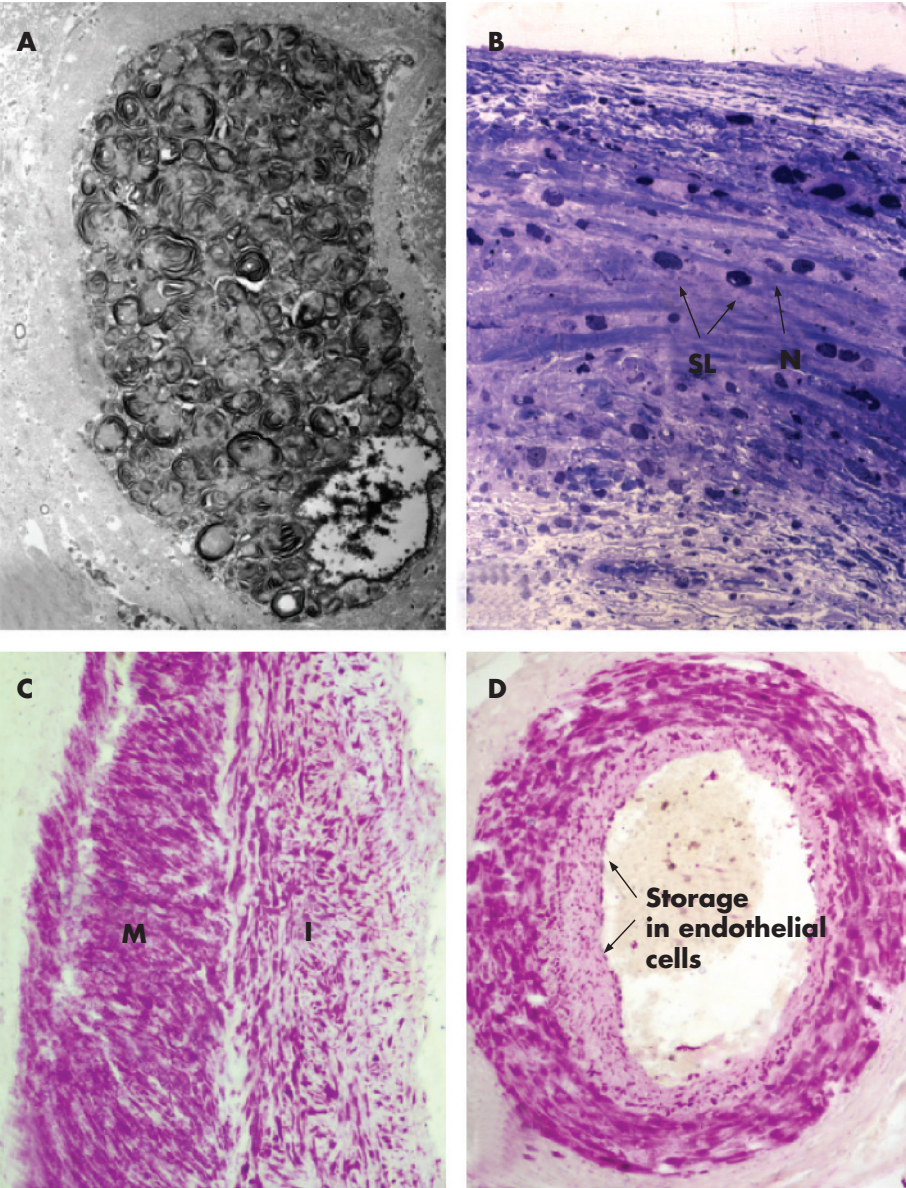
Figure 3 (A) Electron microscopic image of a valvular fibroblast loaded with stored glycolipid. (B) Semithin plastic embedded section of a mitral valve stained with alkaline toludene blue. Dark blue deposits demonstrate the stored lysosomal glycolipid (N, nuclei; SL, storage lysosome). (C) Sample of the left main coronary artery loaded with PAS + glycolipid in medial (M) and intimal (I) cells (longitudinal section). (D) Transverse section of a small subepicardial branch of a coronary artery loaded with PAS + glycolipid. Bulk of PAS positivity (panels C and D) was easily removed by pre-extraction using chloroform-methanol mixture. Images courtesy of Milan Elleder, Charles University, Prague, Czech Republic.

Table 3 Major clinical studies examining the prevalence of AFD among patients with unexplained left ventricular hypertrophy or hypertrophic cardiomyopathy

Study	n, sex	Population	Age mean (SD) (range)	Prevalence n (%)
Nakao et al[2]	230 men	Consecutive, unexplained hypertrophy (IVS and/or PW ⩾13 mm)	62 (13) (55–72)	7 (3.0%)
Sachdev et al[3]	74 men	HCM diagnosed at <40 years of age (maximum wall thickness ⩾13 mm)	26 (9) (8–39)	1 (1.4%)
	79 men	HCM diagnosed at ⩾40 years of age (maximum wall thickness ⩾13 mm)	53 (8) (40–71)	5 (6.3%)
Arad et al[11]	75 (45 men)	Unexplained hypertrophy—HCM (wall thickness ⩾13 mm)	ND (12–75)	0 (0%)
	20 (NG)	HCM—massive LVH (wall thickness ⩾30 mm)	ND (9–58)	0 (0%)
	24 (NG)	HCM with pre-excitations (short PR, delta wave)	ND (8–42)	0 (0%)
Ommen et al[5]	100 (44 men)	Consecutive patients referred for septal myotomy—myectomy for LVOT obstruction	45 (17) at diagnosis (ND)	0 (0%)
Chimenti et al[4]	34 women	Consecutive, unexplained LVH (wall thickness ⩾13 mm)	50 (14) (ND)	4 (12%)
	62 men	Unexplained LVH (wall thickness ⩾13 mm)	ND	2 (3.3%)

HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; ND, no data; NG, not given; PW, posterior wall.
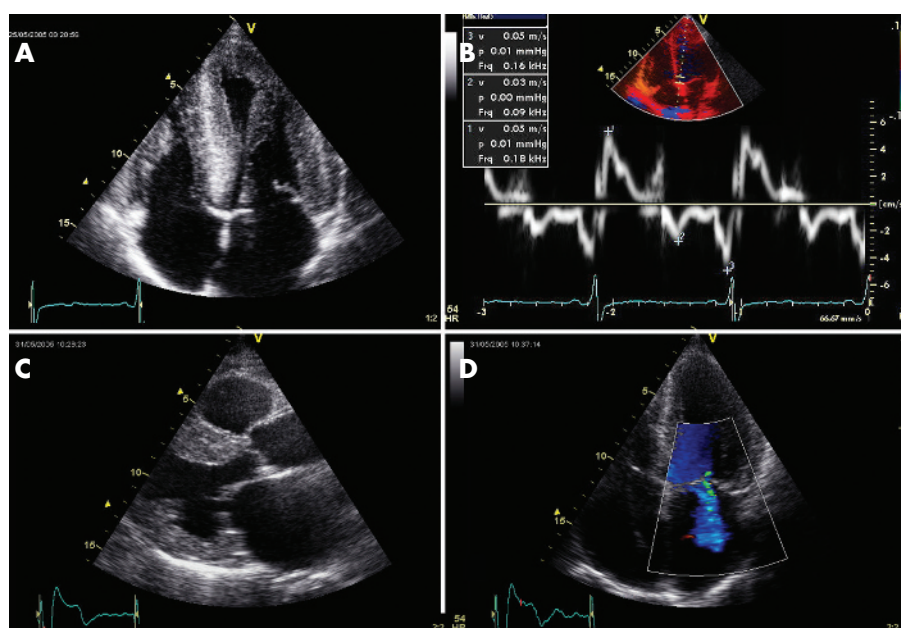
Figure 4 Echocardiographic images illustrating typical findings in patients with Anderson-Fabry disease. (A) Apical four-chamber view illustrating a severe left ventricular hypertrophy, right ventricular hypertrophy and mild bilateral atrial dilatation. (B) Tissue Doppler recording of the septal annular mitral velocities showing a significantly decreased early diastolic and systolic annular velocity. (C) Parasternal long axis view showing moderate left ventricular hypertrophy, mitral valve thickening and moderate left atrial dilatation. (D) Colour Doppler imaging in the same patient as on panel C, illustrating the presence of the mild mitral regurgitation. Bilateral atrial dilatation is evident and pacemaker electrode is present within the right ventricle.

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Most patients (male and female) with AFD develop LVH (fig 4).[1][6] Early disease is characterised by concentric remodelling, progressing later to concentric hypertrophy. Asymmetric septal hypertrophy, indistinguishable from that seen in sarcomeric cardiomyopathies, accounts for 5% of cases. Dynamic left ventricular outflow obstruction is rare, but does occur.[3][6][9] The right ventricle is often affected, but this does not appear to have major functional or clinical consequences.

Conventional measures of left ventricular systolic function are usually within the normal range.[6] Nonetheless, studies using tissue Doppler imaging and strain-rate imaging have demonstrated reductions in systolic performance, occurring earlier in the longitudinal than in the radial dimension.[10] Mild diastolic dysfunction is a common feature of AFD, but rarely causes restrictive pathophysiology except in the most advanced stages of the disease associated with pronounced fibrosis.[6][7]

Valve disease

Valve disease in AFD is caused by infiltrative changes within valvular fibroblasts (figs 3 and 4). Although pulmonary valve involvement is reported, clinically significant changes are most frequently found on left heart valves, probably due to higher haemodynamic stress. In early reports, mitral valve prolapse was said to be common, but recent studies using two-dimensional imaging suggests that it is relatively rare.[6] Typically, valves are thickened and distorted, resulting in mild-to-moderate regurgitation; severe valve disease requiring surgical correction is infrequent. Aortic root dilatation is a feature in some patients and may contribute to aortic valve insufficiency.[6]

Myocardial ischaemia

Early studies suggested a high frequency of ischaemic events in patients with AFD. Contemporary data from registries suggest a low incidence of myocardial infarction, but show that angina and chest pain are frequent, particularly in patients with LVH.

Studies using positron emission tomography have shown that patients with AFD and angiographically normal coronary arteries have reduced coronary flow reserve suggesting that microvascular angina may be responsible for exertional symptoms in some patients.[8] Cases of vasospastic angina are also reported.

Electrophysiological abnormalities

Most adult patients with AFD have an abnormal resting ECG. The most common abnormalities are voltage criteria for LVH and repolarisation changes. Many patients have a short PR interval probably caused by accelerated AV conduction in the majority. With disease progression, patients develop bundle branch block, AV conduction delay and progressive sinus node dysfunction.[11]

Patients with AFD often complain of palpitations. The most frequently encountered rhythm abnormalities are supraventricular tachycardias, atrial fibrillation and atrial flutter.[11] Non-sustained ventricular tachycardia during 24 hour Holter recordings occur in up to 8.3% of patients and individual cases of fatal malignant arrhythmias resistant to ICD implantation are reported.

Anderson-Fabry disease: key points

► Anderson-Fabry disease is an X-linked lysosomal storage disorder caused by deficient activity of the enzyme α-galactosidase A

► Anderson-Fabry disease accounts for at least 3% of unexplained left ventricular hypertrophy in middle aged men

► Disease in the heart is characterised by progressive left ventricular hypertrophy, myocardial fibrosis, and systolic and diastolic dysfunction

► Arrhythmia and conduction disease are common in older patients and may cause stroke and sudden death

Treatment of Anderson-Fabry disease
General measures

Patients with chest pain should receive conventional anti-anginal treatment with the proviso that β-blockers may aggravate the tendency of some patients to symptomatic bradycardia and atrioventricular (AV) conduction block. Our own experience suggests that dihydropyridine calcium channel blockers are relatively effective and safe. Antiplatelet treatment should be offered to all symptomatic patients.

Conventional treatment with ACE inhibitors and diuretics should be used in patients with evidence for systolic impairment; ACE inhibitors (or angiotensin receptor blockers) should be considered in any patient with proteinuria or renal insufficiency. Patients with advanced congestive heart failure may be candidates for heart transplantation, as the intrinsic enzyme production within the graft should prevent reoccurrence of disease.

Many patients in advanced stages of the disease may require pacemaker implantation due to conduction abnormalities. In patients with supraventricular rhythm disturbances, anti-coagulant treatment should be initiated. Subjects with documented malignant ventricular arrhythmias may benefit from implantable cardioverter-defibrillator (ICD) implantation.

There are few data on the management of outflow tract obstruction in AFD, but septal alcohol ablation has been used to good effect. Other treatment modalities (surgical myectomy, dual chamber pacing) may also be appropriate in symptomatic individuals.

Enzyme replacement therapy

Two recombinant enzyme preparations are approved for the treatment of AFD in Europe. *Agalsidase–alfa* is produced in human fibroblasts and is administered in a dose of 0.2 mg/kg of body weight every second week in intravenous (iv) infusions of 40 min. Most patients do not require any premedication.[12] *Agalsidase–beta* is produced in a Chinese hamster ovarian cell line, administered also on a biweekly basis, but in a dose of 1 mg/kg in a 4–6 h iv infusion. Premedication with paracetamol may be required to prevent infusion reactions.[13]

Enzyme uptake is mediated by mannose-6-phosphate, mannose and asialoglycoprotein receptors. Thus, the rate of cellular uptake and tissue specificity depend on the glycosylation and phosphorylation characteristics of the enzyme protein, which differ between the two commercially available enzymes as post-translational protein modifications are species specific. Antibodies have been detected in male patients following the administration of both preparations; their effect on treatment efficacy and tolerability is not clear.

Several trials have shown that both preparations improve neurological and renal manifestations of the disease as well as quality of life.[12 13] A phase 3 trial using agalsidase-alfa has demonstrated an improvement in QRS complex duration.[12] and Gb$_3$ clearance from vascular endothelial cells.[13] Case reports and observational clinical studies have reported improvements in left ventricular structure and function with both treatments.[10 14] Definitive proof of the long term beneficial effects of enzyme replacement therapy on the heart are awaited.

As discussed previously, mutations in the α-galactosidase A gene exert their effect on the substrate protein in a number of different ways, including abnormal protein folding. In cultured cells, galactose and other reversible competitive inhibitors of α-galactosidase A act as chemical "chaperones" that stabilise the enzyme sufficiently to allow its egress from the endoplasmic reticulum and transportation to the lysosome. Once in the lysosome, these inhibitors are competitively displaced from the active binding site by glycosphingolipid. In a single report of a middle aged male with cardiac variant disease, treatment with intravenous galactose (a competitive inhibitor of α-galactosidase A) resulted in an improvement in symptoms and left ventricular function.[15] The therapeutic effect of more easily administered chaperones is being investigated.

CARDIAC DISEASE IN OTHER LYSOSOMAL STORAGE DISORDERS
Glycogen storage diseases

While glycogen synthesis occurs only in the cellular cytoplasm, degradation occurs in cytoplasm and in the lysosomal compartment. These degradation pathways are not functionally connected and decreased activity of an enzyme in one or other pathway leads either to lysosomal or cytoplasmic storage. Lysosomal storage associated with cardiac involvement is found in GSD type IIa and IIb (Pompe and Danon disease, respectively).

Pompe disease

Pompe disease (synonyms: acid maltase deficiency, glycogen storage disease IIa) is an autosomal recessive disorder with infantile, juvenile and adult variants, each differing with respect to the age of onset, rate of disease progression and extent of tissue involvement. The infantile and childhood forms are characterised by myocardial glycogen deposition, massive cardiac hypertrophy and heart failure. The infantile form presents in the first few months of life with severe skeletal muscle hypotonia, progressive weakness, cardiomegaly, hepatomegaly and macroglossia. Left ventricular outflow obstruction is described in about 6% of patients.[16] The ECG typically shows broad high-voltage QRS complexes and short PR interval with a pre-excitation pattern. The disease is usually fatal before 2 years of age due to cardiorespiratory failure. In the juvenile and adult onset variants it is usually limited to skeletal muscle, with a slowly progressive proximal myopathy and respiratory muscle weakness.[16] Recent studies using recombinant enzyme replacement in the infantile and childhood forms have shown LVH regression and improved survival.[17]

Danon disease

Danon disease (synonyms: LAMP-2 deficiency, glycogen storage disorder IIb) is an X-linked deficiency of lysosome associated membrane protein type 2 (LAMP-2). The age and presentation of the disease is variable, with later onset and milder severity in heterozygous females. The typical phenotype of the disease includes skeletal myopathy, mental retardation and cardiomyopathy. Early death in affected males occurs usually between the second and third decade. Cardiac involvement is characterised by LVH, pre-excitation pattern and congestive heart failure. The pathological hallmark of the disease is the presence of intracytoplasmic vacuoles containing autophagic material and glycogen in cardiac and skeletal muscle cells. Disease clinically confined to the heart is described in some cases with later onset.[18]

Mucopolysaccharidoses

Mucopolysaccharidoses (MPS) are a large group of storage diseases caused by a defect of intralysosomal degradation of acid mucopolysaccharides (glycosaminglycans). Seven main forms and several subtypes can be distinguished. Cardiac involvement is detectable in more than two thirds of affected children. The most common abnormalities occur in the valves with mitral and aortic valve thickening resulting in regurgitation and stenosis. The overall prevalence of valve abnormalities ranges from 27–90% depending on disease subtype (highest frequency in MPS I, II and VI, lowest in type IV and III). As in most lysosomal diseases, the involvement is progressive with age.[19] Coronary involvement with intimal infiltration by storage cells is reported in more than 40% of patients, although rarely results in clinical or electrocardiographic evidence of myocardial ischaemia. The aorta may also be affected.[19]

Myocardial changes in MPS include interstitial infiltration and fibrosis. LVH, dilated cardiomyopathy and endomyocardial fibroelastosis are described. Cases of conduction system dysfunction are also reported and sudden cardiac deaths are relatively frequent. Enzyme replacement therapy is available for MPS type I, II and VI.

Sphingolipidoses
Gaucher disease

Gaucher disease is the most frequent sphingolipidosis. It is caused by a deficiency in β-glucocerebrosidase leading to lysosomal accumulation of glucocerebroside within macrophages. Lipid-laden macrophages (Gaucher cells) accumulate within the reticulo-endothelial system resulting in hepatosplenomegaly, bone marrow replacement, anaemia and thrombocytopenia and skeletal abnormalities. The disease is subclassified according to the onset and severity of the neurological involvement. Valvular and aortic calcification, heart failure and pericarditis are reported but the heart is not involved in most patients. More importantly, pulmonary hypertension occurs in up to 30% of untreated patients. Successful treatment appears to reduce the prevalence to 7.4%.[20]

Niemann-Pick disease

Niemann-Pick disease is caused by a deficiency in acid sphingomyelinase. It is subclassified into type A (infantile, neurodegenerative) and type B (later onset of hepatosplenomegaly, pulmonary involvement, survival into adulthood). Niemann-Pick types C and D represent distinct genetic and metabolic defects. Cardiac involvement is rare.[20]

CONCLUSIONS

Anderson-Fabry disease is an important differential diagnosis in middle aged and elderly patients with unexplained LVH. Emerging evidence suggests that enzyme replacement therapy substantially improves many of the features of the disease, including some aspects of cardiac involvement. The advent of new enzyme replacement therapies offer the prospect of a similar improvement in quality of life and prognosis for patients with other lysosomal storage disorders.

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